Low molecular weight heparin (enoxaparin) in the management of unstable angina: the ESSENCE study

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The evidence that aspirin improves outcomes in unstable angina is both clear and overwhelming.[1] The same cannot be said for the combination of aspirin and unfractionated heparin (UFH) compared with aspirin alone. All the trials conducted in this area have been underpowered to detect significant difference in the risk of death, myocardial infarction (MI), and recurrent ischaemia.[2–4] A pooled analysis does suggest that UFH is superior to placebo in the presence of aspirin,[5] but no single trial has been able to confirm this, nor have trials of sufficient size been performed. Treatment with UFH is associated with a significant failure rate, for which a number of explanations have been suggested. Firstly, the anticoagulant effect of UFH is unpredictable and, despite regular monitoring, many patients are not maintained within the optimum activated partial thromboplastin time (aPTT) range of 1.5–2.5 times control. Secondly, UFH is susceptible to binding by plasma proteins and neutralisation by platelet factor IV. Thirdly, a rebound phenomenon has been identified after the cessation of UFH. This has been demonstrated, especially in the absence of aspirin.[3 6] Fourthly, the antiplatelet effects of aspirin may be overcome in the presence of a potent stimulus from disrupted plaque.

Low molecular weight heparins (LMWHs) have advantages over UFH that may result in greater efficacy and safety, as well as the practical advantages of subcutaneous administration and a predictable anticoagulant effect that removes the need for monitoring. The ESSENCE trial was designed to compare the safety and efficacy of enoxaparin with UFH in patients with unstable angina and non-Q wave myocardial infarction. Enoxaparin is an LMWH with a different chain length and anti-IIa:anti-Xa activity profile compared to other LMWHs.

Methods

The ESSENCE study was a double blind, prospective, randomised trial of 3171 patients recruited from 176 centres in the US, Canada, South America, and Europe. Male and non-pregnant female adults over the age of 18 years were eligible for enrolment. A history of angina at rest lasting for at least 10 minutes during the 24 hours before randomisation was required, as well as evidence of underlying ischaemic heart

Table 1 Triple end point rates (death, MI or recurrent angina)

Time	*UFH (n = 1564)*	*Enoxaparin (n = 1607)*	*Relative risk reduction (%)*	*p Value*
48 hours	115 (7.4)	99 (6.2)	16.2	0.176
14 days	309 (19.8)	266 (16.6)	16.2	0.019
30 days	364 (23.3)	318 (19.8)	15.0	0.017

Values are n (%).

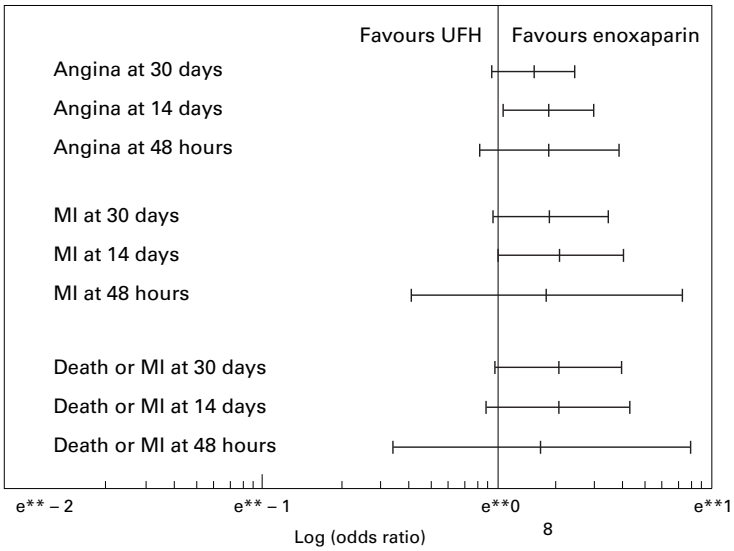

Figure 1 Odds ratios for individual end points in ESSENCE.

Trial acronyms

ESSENCE: Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events
FRAXIS: FRAXiparin in Ischaemic Syndromes
FRIC: FRagmin In unstable Coronary artery disease
FRISC: FRagmin during InStability in Coronary artery disease
GUSTO: Global Use of Strategies To Open occluded coronary arteries
OASIS: Organization to Assess Strategies for Ischaemic Syndromes
PURSUIT: Platelet IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy
PARAGON: Platelet IIb/IIIa Antagonists for Reduction of Acute coronary syndrome events in a Global Organization Network
PRISM: Platelet Receptor Inhibition in ischemic Syndrome Management
PRISM PLUS: Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms
TIMI: Thrombolysis In Myocardial Infarction

Table 2 Revascularisation rates at 30 days

Procedure	*UFH (n = 1564)*	*Enoxaparin (n = 1607)*	*Relative risk reduction (%)*	*p Value*
CABG	214 (13.7)	198 (12.3)	10.0	0.254
PTCA	293 (18.7)	236 (14.7)	21.6	0.002
Total	504 (32.2)	434 (27.0)	16.0	0.001

Values are n (%).
CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.
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disease (ECG changes, history of previous MI or revascularisation, or invasive or non-invasive test results suggesting ischaemic heart disease). Patients who satisfied the inclusion criteria were randomised to receive either enoxaparin, 1 mg/kg subcutaneously every 12 hours, plus placebo bolus and infusion, or UFH (bolus and infusion, dose adjusted according to aPTT) and subcutaneous placebo injections. Anticoagulant treatment continued for a minimum of 48 hours and a maximum of eight days, according to the patient's condition and the physician's preference. All patients also received oral aspirin. The primary end point was a composite of the incidence of death, MI, or recurrent angina at 14 days. The incidence of the same composite end point at 30 days and one year constituted secondary end points.

Results

EARLY FINDINGS

At least one dose of study drug was received by 98% of enrolled patients, and the mean duration of treatment was 2.6 days for both groups. The early results (14 and 30 days) of the ESSENCE trial have been reported elsewhere[7]; a summary of the efficacy results is shown in table 1. At 48 hours, a relative risk reduction of 16% was evident in patients treated with enoxaparin and this was sustained through to 14 and 30 days. The difference between the two treatment arms was highly significant at 14 and 30 days. A more detailed analysis shows that the risk reduction is spread evenly across each individual end point (death/MI, MI, or recurrent angina); risk reduction is similar for each one of the components of the triple end point (fig 1). The incidence of major haemorrhage was similar in the two treatment groups (6.5% enoxaparin, 7% UFH), although there was an excess of minor haemorrhages, mainly at injection sites, in patients receiving enoxaparin (18% *v* 14%, respectively).

The rate of revascularisation at 30 days was also significantly lower in patients receiving enoxaparin (table 2). This finding was largely caused by a reduced rate of percutaneous transluminal coronary angioplasty (PTCA) among patients receiving enoxaparin (risk reduction 21.6%). Despite the double blind trial protocol, all countries, including those with high intervention rates such as the US, reported a lower rate of revascularisation in patients treated with enoxaparin.

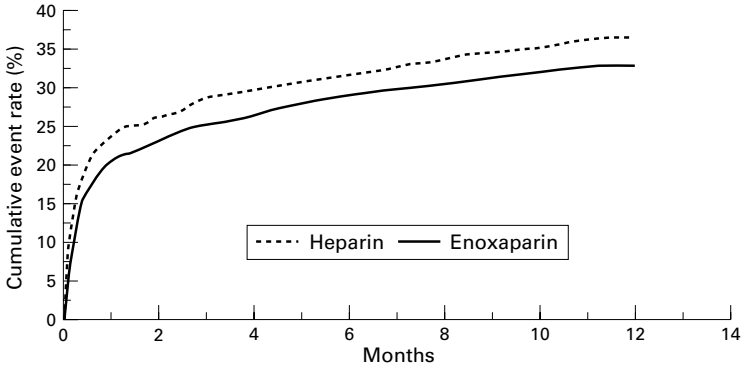

Figure 2 Cumulative event rates for triple end point for enoxaparin and UFH at one year follow up.

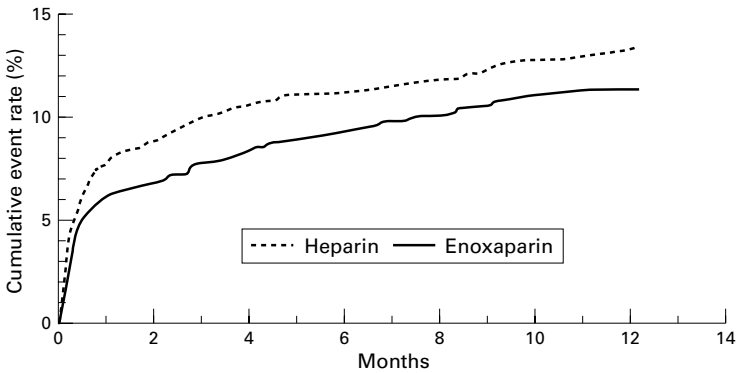

Figure 3 Cumulative event rates for double end point of death or MI for enoxaparin and UFH at one year follow up.

FINDINGS AT ONE YEAR FOLLOW UP

One year follow up data[8] were obtained for 94% of patients with respect to mortality data, and 92% of patients with respect to all cardiac events. For the triple end point, the relative difference between enoxaparin and UFH seen at 30 days (19.8% *v* 23.3%) was fully maintained at one year, with rates of 32% and 35.7%, respectively (p = 0.022) (fig 2). For the double end point of death or MI, the difference between treatment groups at 30 days (6.2% *v* 7.7%) was also fully maintained at one year (11.5% enoxaparin *v* 13.5% UFH, p = 0.082) (fig 3). Although this difference was not significant, there is an actual difference of 2% less in death and MI in the enoxaparin treatment arm (approximately 20 patients per 1000). The ESSENCE trial was not powered for death/MI. However, the difference between treatment arms appears to be of the same order as the benefits observed in early trials of thrombolytics.[9] Further confirmation is required from the TIMI 11B trial.

Discussion

The ESSENCE study was double blind and prospective. It used a double dummy protocol, whereby all patients received one active treatment and one placebo, to ensure that investigators remained unaware of which treatment their patients received. Blinding remained in place until after the one year follow up survey to eliminate the possibility of investigator bias. Although the duration of treatment was short (range 2–8 days, median 2.6 days), the early benefits of treatment with enoxaparin were fully maintained at one year. The study does not establish whether longer periods of treatment confer additional benefit. These results present a contrast to those of two other major trials of LMWHs, FRIC and FRAXIS.[10 11]

These two studies used different LMWHs, dalteparin and fraxiparin, and compared them with UFH. In FRIC, there was no significant difference between dalteparin and UFH at any time, although the earlier FRISC trial had shown benefits for dalteparin against placebo.[12] The results of FRIC may have been influenced by sample size and trial design. With only 1400 patients, this study was underpowered and was open during the early period of five to seven days. Other trials such as GUSTO IIb and OASIS have shown that the majority of events occur during this time.[13 14]

The potential impact of the benefits of enoxaparin need to be seen in the context of other trials in unstable angina and non-Q wave MI. The benefits achieved are over and above the important impact of aspirin in almost halving the risk of cardiac events. More recently, glycoprotein (GP) IIb/IIIa receptor inhibitors have been introduced and used as adjunctive treatment in patients undergoing PTCA. These agents block the final common pathway of platelet aggregation and potentially offer considerable benefits in unstable angina and non-Q wave MI. Their largest impact is seen in the highest risk patients and in the context of intervention. Some trials of GP IIb/IIIa receptor inhibitors have allowed for the possibility of conservative treatment, with intervention (angiography with or without PTCA; stenting) not forming an obligatory part of the protocol. In the PURSUIT trial,[15] the absolute difference between treatment arms at 30 days for the rate of death or MI was 15 per 1000 patients. An analysis of pooled data from four trials—PURSUIT,[15] PARAGON,[16] PRISM,[17] and PRISM PLUS[18]—shows that the net impact of GP IIb/IIIa receptor inhibitor treatment was a reduction in the rate of death or non-fatal MI of 16 patients per 1000 at 30 days. These results appear to be of a similar order of magnitude to the ESSENCE results reported here. It may well be that these two classes of agents—LMWH and GP IIb/IIIa receptor inhibitors—could act in a synergistic fashion. Although no trials combining these agents have been performed yet, this will be an intriguing avenue for future research.

Conclusions

Currently, standard treatment for patients presenting with acute coronary syndromes includes a combination of oral aspirin and intravenous UFH, but this regimen fails to prevent further ischaemic events in a substantial number of patients. LMWHs offer a number of advantages over UFH, including reduced binding to plasma proteins, greater resistance to inhibition by platelet factor IV, and a longer plasma half life. These properties result in good bioavailability after subcutaneous administration, with a predictable anticoagulant effect that removes the requirement for aPTT monitoring.

ESSENCE is the first large scale study to show that short term treatment with an LMWH offers long term benefits in acute coronary syndromes, and these findings have practical implications for patient management. For patients with unstable angina or non-Q wave infarction who are judged to be at high risk of further events, recommended treatment regimens are likely to include subcutaneous LMWH in preference to UFH. Combination with a GP IIb/IIIa receptor inhibitor may confer further advantage, but this approach requires testing. More information about the effects of both short and long term enoxaparin treatment will be available when the TIMI 11B study is reported.

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